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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/605,708	GONG ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-15,20,21,24,30-32 and 35-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-15,20,21,24,30-32 and 35-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09913898.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and response filed January 9, 2008 and subsequent supplemental response filed February 20, 2008 have been received and entered. Claims 1, 2, 9, 15, 20, 21, 24, 24, 36 and 41 have been amended, while claims 4-8, 16-19, 22-23, 25-29 and 33-34 are cancelled. Applicants have also added claims 43-45 generally directed to elected invention.

This action is non Final.

Election/Restrictions

Applicant's election of claims 1-16, 20-21, 29-32 and 35-41 in the reply filed on January 19, 2006 was acknowledged. The applicants elected muscle specific promoter examination. It was noted claim 19 included muscle specific promoter and therefore claim 19 was rejoined with elected groups. Additionally, claim 24 was also rejoined for the examination purposes to the extent it read on elected invention.

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 are currently under examination.

Oath/Declaration

The Gong declaration filed on February 20, 2008, is sufficient to overcome the rejection of claims 1-8, 16, 20, 21 and 36-42 based upon the references applied under 35 U.S.C. 103(a).

New Grounds of Claim Rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicants' argument filed on 1/9/2008 and 2/20/2008 has been fully considered and persuasive to the extent claims are now limited to the indicated enabled scope set forth at page. It is noted that applicants have argued and provided evidence indicating that transgenic zebrafish line generated by Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS) and cited by Examiner that comprises a fluorescent gene under the control of beta actin promoter (page 295, col. 1, para 2, Fig 4) could not be viewed in sunlight (see the email of Dr. Hitoshi Okamoto and applicants" argument page 9, para. 1-3). In view of applicants' newly submitted evidence and upon further consideration instant scope of enablement has been modified to reflect a modified enabling scope for claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45.

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for

(1) a method of providing transgenic fish to the ornamental fish market comprising the step of

(a) obtaining a stable germline transgenic ornamental fish comprising a chimeric gene comprising a promoter that drives the expression of a fluorescent protein selected from a group consisting of BFP, YFP, CFP and GFPin muscle cells of said fish, said promoter being fast skeletal muscle isoform of myosin light chain 2 gene promoter comprising SEQ ID NO:22,

wherein said transgenic fish expresses fluorescent protein encoded by fluorescent gene in skeletal muscle at a level sufficient such that said transgenic fish exhibit visible fluorescence upon exposure to sunlight , and

(b) distributing said fish to the ornamental fish market.

does not reasonably provide enablement for using any other muscle specific promoter to obtain stable transgenic fish line suitable for ornamental fish market showing fluorescence upon exposure to sunlight or any transgenic fish showing

more than one fluorescent protein in the same tissue to effect a new fluorescent color that is visible after exposure to sunlight or mating fish across genera or family. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

These claims embrace obtaining transgenic fish line comprising fluorescent gene under control of any muscle specific promoter such that fish express protein at level sufficient upon exposure to sunlight and distributing said fish to the ornamental fish market. Additionally, claims are also directed to method wherein transgenic fish are displayed under ultraviolet or blue light.

Prior to instant invention, transgenic fish that are capable of expressing heterologous gene under the control of different promoter including muscle specific promoter were generally known in prior art (see Moss et al, Higashijima et al, Kuo et al, Kim et al, Hackett et al, all art of record). The teaching in prior art shows that in spite of these constructs being reproducibly expressed in tissue specific manner, none of these promoters were suitable for use in generating transgenic ornamental fish because an unusually high level of expression is required in the muscle tissue to be of commercial or ornamental value.

The specification describes generating stable germline transgenic zebrafish using a 2kb MLC2f promoter fragment and transient transfection assays using several constructs comprising smaller fragments of the MLC2f promoter. However, only two-construct containing promoter fragments (2011 bp and 1338 bp) are capable of maintaining a high level of expression and only the 2011bp fragment resulted in fluorescence in transient and stable transgenic zebrafish that can be observed upon exposure to sunlight. The specification teaches generation of a green fluorescent transgenic fish line comprising chimeric fluorescence gene under the control of the 2011 bp MLC2f promoter, wherein transgenic founder and F1 stable germline transgenic offspring zebrafish containing pMLC2f-EGFP emit a strong green fluorescent light under a blue or ultraviolet light (see figure 11 A and B) as well as sunlight (see paragraph [0089]). In fact, specification teaches that the expression of GFP using pMLC2f-EGFP is much higher than that obtained using the pMCK-EGFP (See example 3) that contains a 1.5 kb of zebrafish MCK promoter.

Thus, the specification has only identified limited species of pMLC2f-EGFP that contains SEQ ID NO: 22 showed strong enough fluorescence expression, which could be observed when the fish are exposed to sunlight. While the specification has contemplated that methods of the invention may be used to create transgenic fish of any species using any muscle specific promoter, the guidance provided by the

specification correlated to generation of zebra fish founder and offspring comprising pMLC2f-EGFP that showed strong green fluorescence expression when fish are exposed to normal sunlight.

The specification exemplified GFP transgenic fish emits green fluorescence light under a blue or ultraviolet light and this feature makes the genetically engineered fish unique and attractive in the ornamental fish market (see paragraph 13 of the published application). Based on the applicant's disclosure it appears that the intended purpose of obtaining transgenic fish is to provide fluorescent fish to ornamental fish market for display purposes. Furthermore it is generally known in the art and described by applicants that ornamental and aquarium fish are defined as fish that are produced and maintained solely for exhibit purpose (see applicants' argument and FDA fish classification Guide, filed 8/11/2006, page 13, art of record). Prior art teaches numerous factors that potentially affect the transgenic frequency or expression levels in transgenic fish including (i) expression levels that do not strongly correlated to transgenic frequency; and (ii) placement of construct (Higashijima et al Dev Biol. 1997; 192(2): 289-99; art of record). The intent is not to say that transgenic fish comprising fluorescent gene cannot be made rather art of making transgenic ornamental fish for the distribution in ornamental fish market is unpredictable and dependent on a strong promoter that works well in different species of fish and capable of showing high level of fluorescent gene expression. The specification has provided a working example correlating only to specific region of muscle specific MLC2f promoter that conferred the expression that could be observed when the fish is exposed to sunlight. Prior to instant invention, transgenic fish that are capable of expressing heterologous gene were generally known in prior art (See Higashijima, IDS; Kuo et al, 1995, Kim et al, 1996, Hackett et al 1993; all of the record). However, in all instances, the transgenic fish displayed expression of transgene or fluorescent protein that was visible only under microscope. Moreover none of previously developed transgenic lines displayed expression or fluorescent

color visible to unaided eyes. In fact, applicant's own post filing art, describes the problem in generating transgenic fish suitable for ornamental fish market. Specifically Gong et al (Biochem Biophys Res Commun. 2003; 308(1): 58-63, art of record) state availability of several GFP transgenic zebrafish that have been produced using many different tissue-specific including muscle specific promoters (also see references therein), but none of these transgenic lines display fluorescent color visible to unaided eyes. Thus, one key to success in the generation of colorful transgenic ornamental fish is in the strength of the promoter. Another factor is the selection of tissue; the muscle constitutes majority of the body and thus synthesizes more and visible color proteins. In contrast, transgenic GFP expression in only a single layer of skin cells cannot be visualized without using a fluorescent microscope (Gong et al, supra, page 62, col. 2, para. 1)". It is noted that applicants have described in spite of availability of several transgenic line that uses tissue specific promoters, none of these transgenic fish made by using tissue specific promoter were suitable for ornamental fish market. Gong et al clearly suggest importance of strength of the promoter in obtaining transgenic fish suitable for ornamental fish market. It is apparent that choice of a promoter could greatly effect the level of expression in transgenic ornamental fish. It is clear from the teaching of Gong et al that strong expression of fluorescent gene under the control of MLC2 promoter in muscle tissue that constitutes majority of the fish body tissue is vital for successfully generating transgenic fish for distribution in ornamental fish market. In the instant case, claims are drawn to obtain a transgenic fish comprising chimeric genes under control of any muscle specific promoter that drives the expression of a fluorescent protein and distributing such fish in ornamental fish market. It is apparent from the teaching of Gong et al that generation of transgenic fish that is suitable for distribution in ornamental fish market requires strong muscle specific promoter, which may require exposure of fish to a light of specific wavelength selected to be optimal for the fluorescent protein in order to visualize

fluorescence on the fish. In view of foregoing discussion it is apparent that specification has failed to provide relevant teachings or specific guidance correlating to transgenic fish comprising fluorescent gene under control of any muscle specific promoter other then exemplified muscle specific promoters that are suitable for generating transgenic ornamental fish intended for distribution in ornamental fish market showing contemplated biological activity. In fact, the prior art , specification and post filing art reports that not all muscle specific promoters function would function in same manner as descibed in the specification and it would be unpredictable which fragment of other tissue specific promoter would show higher level of expression in muscle tissue that constitutes majority of the fish body tissue is key to success in generating transgenic fish for ornamental fish market (supra). It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991).

Given the differences in the expression of a fluorescent gene as embraced by the claims, particularly when taken with the lack of guidance provided by the specification, it would require undue experimenattaion to emperically test different muscle specific promoter or promoter regions, level of the fluorescent gene expresion, the conseqeunce of that expresion and therefore its suitability for distribution in ornamnetal fish market. The cited art of Gong et al and references therein clearly shows that obtaining transgenic fish comprising fluorescent gene required strong muscle specific promoters for displaying fluorescence in order for it to be suitable for distribution in ornamental fish market. In the instant case, the specification has failed to report obtaining a transgenic fish line comprising a gene

encoding a fluorescent protein under the control of any other muscle specific promoter except specifically those exemplified in the instant specification being suitable for distribution to ornamental fish market.

Claims are also directed to creating transgenic ornamental fish that show more than one fluorescent protein in the same tissue upon exposure to sunlight. It is generally known in the art that sunlight is uniform in color and is actually composed of a broad range of radiation wavelengths in the ultraviolet (UV), visible and infrared (IR) portions of the spectrum. Red light consists of light waves with a wavelength of about 700 nanometers (billionths of a meter), yellow light has wavelengths of about 550 nanometers, and blue light has wavelengths of about 450 nanometers. But the wavelengths of colored light are not limited to specific ranges. Thus, claims require expression of plurality of different fluorescent protein in same tissue suggesting intermediate colors of unknown excitation/emission spectra. For instance, waves that have wavelengths of 600, 625, 650, and 675 nanometers would have orange, orangish-red, reddish-orange, and, finally, red colors or other intermediate color combination. These different yet to be discovered color combination may overlap or shift the excitation/emission spectra in sunlight. The guidance provided in the specification is limited to generating transgenic fish expressing GFP (see example 4). The specification and art of record fails to support any other intermediate fluorescent protein or combination of fluorescent protein other than GFP , where emission is visible to the unaided eye.

The claims are also broad in encompassing mating transgenic fish of one species to fish of another species of different and divergent genera and families to obtain the transgenic line comprising one or more chimeric gene under the control of any muscle specific promoter. It is noted that recitation of use of different species encompasses mating fish of different orders, family and genera. The art at the time of filing held that while interspecies crossing within a genus can often occur and can

also be desired, crossing of distantly related species of the same genus as well as crossings of fish between different genera and families are highly unpredictable as to the success of the fertilization, development, health of any progeny that do occur and fertility of offspring. The specification teaches making transgenic fish expressing a transgene encoding a fluorescent protein by microinjection of DNA into the cytoplasm of 1- or 2-cell stage embryos a 1-celled embryo using fish species that lay eggs that are fertilized and develop outside of the mother. The specification teaches operably linking the fluorescent protein-encoding genes to muscle specific MLC2f promoter or MCK promoters that result in expression of the fluorescent protein. The specification teaches crossing the transgenic zebrafish fish to fish of the same wild type species showing similar level of fluorescent expression (See example 3). The guidance provided in the specification is limited to the specification teaching use of closely related Danio (zebrafish) species of fish. The specification failed to disclose extrapolating the same teaching to live bearing fish either in transgenesis or in crossing to obtain the transgenic offspring. It is noted that at the time of filing of this application, Bartley et al (Reviews in Fish Biology and Fisheries 2001,10: 325–337) report that the results of inter-specific hybridization can be variable and depend on the genetic structure of the parent fish. Bartley et al teaches that inadvertent hybridization and backcrossing can lead to unexpected and undesirable results in hybrid progeny, such as failure to produce sterile fish, loss of color pattern, and reduced viability (see abstract). Bartley et al also discuss hybridization between species often results in offspring that are sterile or with diminished reproductive capacity as a result of problems in gonad development and chromosome pairing (page 330 col. 1, last para, bridging to col. 2). The specification fails to set forth, of the many families of fish, which species of fish would provide valuable hybrid offspring. For example, the specification fails to support that transgenic zebrafish could crossed with any other fish encompassed by the claims such as guppy, Molly or pangasius. Furthermore, it would be unpredictable how

strong MLC2f promoters would be in hybrid species, particularly since art teaches importance of strength of the promoter in obtaining transgenic fish suitable for ornamental fish market. Absent of evidence to the contrary, it is not clear that MLC2f promoter would be functional in hybrid species in the same manner as they have been demonstrated for parent species. The lack of guidance in the specification would force the skilled practitioner to guess and try crossing different species of wild type fish to make transgenic ornamental fish showing no loss of fluorescent color when exposed to ultraviolet or sunlight. Such guessing would require extensive and undue experimentation. Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)*, Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In the instant case, the specification has failed to report obtaining any species of transgenic fish line comprising fluorescent gene under control of any muscle specific promoter other then those specifically exemplified for zebra fish comprising chimeric gene under control of MLC2f promoter (SEQ ID NO: 22) that drives the expression of fluorescent protein wherein said transgenic fish shows fluorescence upon exposure to sunlight that is suitable for distribution to ornamental fish market.

In conclusion, in view of breadth of the claims and absence of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions commensurate with full scope of the claim. The specification and prior art do not teach method of obtaining transgenic fish of any species comprising fluorescent gene

under control of any muscle specific promoter and distributing said fish to ornamental fish market commensurate with full scope of the claims. An artisan of skill would have to perform undue experimentation to make and use the invention because the art of making transgenic fish using any promoter for distribution of said fish in ornamental fish was unpredictable at the time of filing of this application as supported by the observations in the art record.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are directed to a transgenic fish line comprising a chimeric gene that is positioned under the control of any muscle specific promoter such that said fish expresses fluorescent protein encoded by the gene in the skeletal muscle upon exposure to sunlight or ultraviolet light. Subsequent claims limit the muscle specific promoter to include zebrafish MCK or zebrafish MLC2 promoter. The specification has disclosed a sequence of a MLC2 promoter and a muscle creatine kinase (MCK)promoter gene. However, guidance of structure function is limited to a transgenic zebra fish line comprising chimeric gene under the control of MLC2f promoter, wherein transgenic founder zebrafish containing pMLC2f-EGFP emit a strong green fluorescent light under a blue or ultraviolet light (see figure 11 A). It is

noted that transgenic offspring obtained after the crossing transgenic founders with wild-type fish also displayed strong green fluorescence (see figure 11B) that was found high enough to show green fluorescence when the fish are exposed to sunlight. While specification teaches that the expression of GFP using the pMCK-EGFP (See example 3) that contains a 1.5 kb of zebrafish MCK promoter, but specification fails to correlate the expression of GFP upon exposure of fish to sunlight.

In analyzing whether the written description requirement is met for the genus claim, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. The claims embrace transgenic fish line of any species that comprises a chimeric gene under the control of any muscle specific promoter showing expression of fluorescent protein upon exposure of any light including sunlight. The specification teaches only two constructs (2011 bp and 1338 bp) that are capable of maintaining the high level of expression, while the highest expression was obtained only with the 2-kb promoter, indicating the importance of the promoter region of 1338 bp to 2011 bp for conferring the highest promoter activity required for strong fluorescence expression upon exposure to sunlight (see para 89 and 90 of the published application). Additionally, specification teaches only one species of transgenic fish line (zebra fish) comprising chimeric gene under the control of one species of muscle specific promoter (MLC2f promoter), wherein the transgenic founder zebrafish containing pMLC2f-EGFP emit a strong green fluorescent light under a blue or ultraviolet light and the transgenic offspring obtained after the crossing transgenic founders with wild-type fish displayed strong green fluorescence that was found high enough to show green fluorescence when the fish are exposed to sunlight. The specification is silent, however, on any other muscle specific promoter or any other variant of MLC2f that would show contemplated biological function of

showing strong expression upon exposure to sunlight. The specification additionally fails to disclose the nature of the association of genus of other muscle specific promoter that would show fluoresce upon exposure to any light. The claims thus constitute a genus that encompasses plurality of different muscle specific promoter or their fragments yet to be discovered, and since the specification only discloses a single species of MLC2f promoter that may be capable of showing fluorescence upon exposure to any light including sunlight, the disclosed structural features of said MLC2f comprising SEQ ID NO: 22 do not constitute a substantial portion of the claimed genus. As such, the Artisan of skill could not conclude that Applicant possessed any additional species, except for that of a zebra fish comprising a chimeric gene under the control of a fast skeletal muscle isoform of myosin light chain 2 gene promoter which includes the sequence of SEQ ID NO:22. Hence, only the transgenic ornamental fish comprising chimeric gene under control of MLC2f promoter could be demonstrated as possessed for the contemplated biological effect.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (Applicants are directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112 ¶1 "Written Description" Requirement, Rev. 1, 2008: at http://www.uspto.gov/web/menu/written.pdf.). Moreover, MPEP 2163 states:[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189: *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus for contemplated biological activity. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims read on using any transgenic fish line comprising chimeric fluorescent gene under control of any muscle specific promoter such that it would express fluorescence upon exposure of said fish to any light including sunlight. The specification has exemplified use of only discloses a single species of MLC2f promoter that may be capable of showing fluorescence upon exposure to any light including sunlight (see example 3). However, specification fails to provide any specific guidance or structure of any other muscle specific that could be used to express fluoresce upon exposure of fish in sunlight. In a post filing art, Gong et al (Biochem Biophys Res Commun. 2003; 308(1): 58-63, art of record) state availability of several GFP transgenic zebrafish that have been produced using many different tissue-specific including muscle specific promoters (also see references therein), but none of these transgenic lines display fluorescent color visible to unaided eyes. Gong et al emphasizes the strength of the promoter as critical aspect in successful generation of colorful transgenic ornamental fish. It is generally known in prior art that several different muscle specific promoters have highly divergent overall structure. The claimed invention as a whole is not adequately described since claims read on genus of muscle specific promoter showing contemplated biological activity and specification fails to describe any other muscle specific promoter other then one exemplified that could show fluorescence upon exposure of fish to sunlight and which is not conventional in the art as of applicants effective filing date. In view of the level of

knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the a transgenic fish line comprising chimeric construct comprising a fluorescent gene under control of any muscle specific promoter . The claimed invention as a whole is not adequately described if the claims require essential or critical elements or which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

The skilled artisan cannot envision the detailed chemical structure of the encompassed coding sequence of heterologous viral envelope other then exemplified MLC2f containing SEQ ID no: 22 showing contemplated biological activity, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a transgenic fish line comprising chimeric fluorescent gene under control of any muscle specific promoter showing contemplated biological activity (showing fluorescent upon exposure of transgenic fish to sunlight) at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Withdrawn-Claim Rejections - 35 USC § 103

The rejection of claims 1-8, 16 and 36-42 under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS) and Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998) is withdrawn in view of amendments to the independent claims. It is noted that applicants have provided declaration to antedate the reference of Bryan. Additionally, applicants have submitted evidence to indicate that transgenic fish disclosed by Higashijima et al do not fluorescence under sunlight (see the email as appendix and applicants' argument).

The rejection of claims 2-3 under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Chalfie, et al Green fluorescent protein: properties, applications, and protocols, Wiley-Liss, New York, 1998), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record) as applied to claims 1, 9-16, 19, 24, 30-32, 35-42 above, and further in view of Abeywickrama et al (US Patent no: 5, 028,839, dated 7/2/1991) is withdrawn in view reasons set forth above.

The rejection of claim 21 under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Chalfie, et al Green fluorescent protein: properties, applications, and protocols, Wiley-Liss, New York, 1998), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record) as applied to claims 1, 9-16, 19, 24, 30-32, 35-42 above, and further in view of Moss et al (Gene. 1996; 173: 89-98, IDS) or Chan et al (Abstract of paper presented at 1994 meeting on Zebrafish development and Genetics, abstract, IDS) is withdrawn in view of reasons set forth above.

The rejection of claim 20 under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Chalfie, et al Green fluorescent protein: properties, applications, and protocols, Wiley-Liss, New York,

1998), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record) as applied to claims 1, 9-16, 19, 24, 30-32, 35-42 above, and further in view of Liao et al (Analytical Biochemistry, 253, 1997, 137-139, IDS) is withdrawn for the reasons set forth in earlier sections.

The rejection of claims 1, 9-16, 19, 24, 30-32, 35-42 under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record), Yang et al (1998; 273(14):8212-6, IDS) and Living Colors Subcellular Localization Vectors (October 1998) CLONTECHniques XIII (4):8-9 is withdrawn in view of reasons set forth above.

New-Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 9-15, 20-21, 24, 30-32, 35-44 and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-53, 58-60, 66-78 of copending Application No. 11/749,032. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of providing transgenic ornamental fish by obtaining transgenic fish comprising one or more fluorescence genes, wherein the transgenic fish expresses one or more fluorescent proteins encoded by the one or more fluorescence genes under control of muscle specific promoter; selecting from said transgenic fish one or more that expresses the fluorescent proteins at a level such that the fluorescence can be observed when the fish are exposed to sunlight; and (c) distributing said selected fish to the ornamental fish market. Claim 43-45 ,1-15 of instant application is directed to a method of providing transgenic fish to the ornamental fish market comprising the step of (a) obtaining a transgenic ornamental fish comprising a chimeric gene comprising a promoter that drives the expression of a fluorescent protein selected from a group consisting of BFP, YFP and CFP predominantly in muscles of said fish, said promoter being a muscle specific promoter, such that said transgenic fish expresses fluorescent protein encoded by fluorescent gene in skeletal muscle at a level sufficient such that said transgenic fish fluoresces upon exposure to one or more light and (b) distributing said fish to the ornamental fish market. Subsequent claims limit the promoter to include MCK (claim 20) and MLC (claim 21). Claims also limit the method of claims to further comprises displaying fish under blue or UV light and wherein fish expresses BFP (claim 9), EBFP (claim 10), YFP or other fluorescent gene set forth in claims 12-14. Claims are also directed to a method wherein the transgenic fish is stable transgenic fish line by breeding the transgenic fish with a second fish to obtain offspring, subsequently limiting the second fish to be selected form a list consisting of different species of fish (claim 36-42), whereas

claims 42-53, 58-60, 66-78 of application '032 application are directed to a same method and offspring produced therefrom by generating a transgenic ornamental fish by obtaining a transgenic fish comprising chimeric fluorescent gene under control of a promoter subsequently limiting to muscle specific promoter that included MCK and MLC promoter. Additionally, claims are also directed to generating stable transgenic ornamental fish by breeding the transgenic fish of the invention with another wild type fish. . Thus, the claims of application no 11/749,032 are structurally similar in scope for obtaining transgenic fish comprising fluorescent gene under control of muscle specific promoter, which encompasses the transgenic ornamental fish as claimed in instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Maintained-Double Patenting

Claims 1-3, 9-16, 19-21, 24, 30-32, 35-42 remain rejected and newly added claims 43-45 are also rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U. S. Patent No. 7,135,613. Applicants argue that during the prosecution of USSN 09/913,898, Applicants attempted to introduce claims consistent with the claims pending in the present application (amendment dated May 9, 2003). In response to this attempted amendment, the Examiner refused entry of the amendment, taking the position that such claims were found not to be drawn to the invention elected in that case, which later became the '613 patent.

In response, it is noted that Applicants attempts to introduce claims consistent with the claims pending in the present were refused by the examiner during the prosecution of USSN 09/913,898 because newly introduced claims were not directed to elected invention. It was indicated in the restriction requirement

sent on 7/30/2003; 12/18/2003 that newly added business method claims are non responsive (MPEP 821.03). It is emphasized that no where during the prosecution of '898 examiner restricted these business method claims. Hence, a double patenting rejection in this application on claims using same product in a method set forth in '898 is proper and therefore is maintained for the reasons of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: In the instant case, even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass a transgenic fish comprising a chimeric gene comprising a muscle specific promoter that drives the expression of a structural gene in said fish, wherein the transgenic fish contains said promoter in germ cells and/or in somatic cells and which is capable of breeding with either a said transgenic fish or a non-transgenic fish to produce viable and fertile transgenic progeny. It is noted that structural gene is specifically exemplified as different fluorescent gene in US patent 7,135,613. Additionally, the only asserted use of the claimed composition in '613 is distribution of the transgenic ornamental fish to ornamental fish market. Therefore, instant claims differ only with respect to a broader scope distributing transgenic fish which encompass those specifically claimed in patent 7,135,613.

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ellenberg, J., et al. (1998) BioTechniques 25: 838–846 teach variants of GFP with red- and blue-shifted fluorescence emissions that have been characterized, and possibly could be used for double labeling with two different-colored fusion proteins.

Bryan et al (US patent 5,876,995)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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